

## Vitiligo in Children: What's New in Treatment?

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### Abstract

Vitiligo is an acquired chronic hypopigmentary disorder, which usually stars in childhood. The Authors discuss a short review of the more innovative therapies for childhood vitiligo.

**Citation:** Gianfaldoni S, Tchernev G, Wollina U, Lotti J, Rovesti M, Satolli F, França K, Lotti T. Vitiligo in Children: What's New in Treatment? Open Access Maced J Med Sci. <https://doi.org/10.3889/oamjms.2018.060>

**Keywords:** Childhood vitiligo; Innovative treatments; Excimer laser; Micro-focused phototherapy; UVA-1 laser; selective sunlight therapy; Immunomodulatory agent; Antioxidants; Low dose medicine; Dead Sea Climatotherapy

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**Received:** 14-Sep-2017; **Revised:** 25-Dec-2017; **Accepted:** 26-Dec-2017; **Online first:** 21-Jan-2018

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**Funding:** This research did not receive any financial support

**Competing Interests:** The authors have declared that no competing interests exist

## Introduction

Vitiligo is an acquired chronic hypopigmentary disorder, which usually stars in childhood. Even if today different kind of therapies, both medical and surgical, are available [1] (Table 1), none of them may be considered as a standard gold treatment for the variable results in term of repigmentation and the risk of side effects.

Fortunately, innovative treatments have been introducing to solve this problem. They consist in either innovation of conventional treatments and real new therapies.

## Innovative phototherapeutic treatments

Among the conventional treatments for childhood vitiligo, phototherapies may be represent the most effective therapies, especially for generalised vitiligo [2].

**Table 1: Current therapeutic options for vitiligo in children**

Calcineurin inhibitors	Immunomodulation	Burning sensation, erythema, transient pruritus; risk of malignancies?
Calcipotriol	Repigmentation, immunosuppression	Transient burning or irritation
Corticosteroids	Immunomodulation	Epidermal atrophy, striae, telangiectasia, glaucoma, tachyphylaxis, hypothalamus-pituitary axis suppression, Cushing's syndrome, growth retardation
Corticosteroids	Immunomodulation	Glaucoma, tachyphylaxis, hypothalamus-pituitary axis suppression, Cushing's syndrome, growth retardation
PUVA (12yo), Topical PUVA, Topical PUVA sol, nbUVB	Repigmentation, immunomodulation	Erythema, itching or burning sensation; chronic actinic damage; psoralen toxicity (nausea, vomiting, abdominal pain, liver toxicity).

In the last decade's new techniques, both natural and artificial, are being introduced to achieve better clinical results in term of repigmentation, with fewer side effects (Table 2).

**Table 2: Innovative modalities of phototherapy**

The Dead Sea
Selective sunlight therapy
Excimer laser/ Monochromatic excimer light (MEL)
Focused microphototherapy
LASER ALBA UVA1 355nm

## Natural exposure to the sunlight at the Dead Sea (“Dead Sea Climatotherapy”)

It is now clear how at the Dead Sea, the sunlight travels below the normal sea level, attenuating the low range of UVB spectrum, which is the non - therapeutic ones. This fact explains how vitiliginous patients show a greater improvement in skin lesions after sunlight therapy in this special geographical area [3]. The therapeutical protocol varies by the characteristics of patients (e.g. skin phototype, age, comorbidities) and of their skin disease. In general, it consists of the daily session, with a gradual increase of the exposure time.

Many data support the efficacy of Dead Sea Climatotherapy (DSC) in inducing repigmentation and, not less important, in improving the quality of life of patients [4].

Interestingly, a study shows the opportunity to combine DSC with the topical application of a pseudocatalase cream, for achieving a faster repigmentation [5]. Pseudocatalase, however, is a controversial issue. One open trial from London, UK [6] and two randomised, double-blind trials – one from Iran and another one from Australia – could not demonstrate any beneficial effect of this compound compared to placebo [7][8].

## Selective sunlight phototherapy

Another innovation is the selective sunlight phototherapy. Recently, a topical cream (PHOTOCIL®) has been introduced to selectively deliver nb - UVB therapy, when exposed to solar ultraviolet irradiation. The cream is composed by diethylamino hydroxy benzoyl hexyl benzoate and by alpha - glucosyl hesperidin, a glucosylated derivative of a natural plant flavonoid, formulated into a water and oil emulsion. It is applied on vitiliginous patches, while a broadband SPF 50 sunscreen is applied on the unaffected skin. The treatment seems to be

effective and safe, providing good results in term of repigmentation [9][10].

## Excimer lasers

Among the artificial radiation therapies, excimer lasers are probably the oldest phototherapy to have been introduced for vitiligo treatment. They consist of xenon chloride lasers, delivering radiation of 308 nm, with a variable spot size (mean value: 15 - 25 mm). The therapeutic protocol varies on the bases of characteristics of patient, disease and delivery system. The therapeutic procedure schedules consist of two sessions in a week for 13 weeks. During the first session, the operator estimates the MED (Minimal Erythema Dose) of the patient in a vitiliginous area, to be able to set the first dose of radiation, corresponding to the MED decreased by 10%. During the following sessions, the dose increases gradually depending on the clinical response [11].

Excimer lasers are proved to be effective for the treatment of localised forms of vitiligo. The rate and speed of repigmentation vary accordingly with the site and duration of the disease. Lesions on the face and neck are highly respondent areas, while extremities show a slower response [12].

The treatment is quite safe. A part of a supposed chronic skin photo - damages, the more common side effects is represented by perilesional hyperpigmentation, burns, and folliculitis.

An excimer laser may be used alone or in association with topical therapies (e.g. tacrolimus, tacalcitol), which seems to provide better results in term of repigmentation [13].

## Narrow - band UVB target phototherapy and narrow - band UVB micro-focused phototherapy

More innovative is the target phototherapy which allows the operator to treat only the hypopigmented areas, sparing the uninvolved skin.

While the mechanisms of action are the same of the classical phototherapy, the target phototherapy acts in a more precise way because, treating only vitiliginous patches, the operator can use a more appropriate dose of energy, leading to shorter duration and less frequent treatment sessions [14]. In the last years, many different target phototherapy devices have been introduced in the clinical practice. Among these, the last frontier of vitiligo therapy is

represented by the BIOSKIN EVOLUTION® device, a cold light generator micro-focused phototherapy (Table 3).

**Table 3: Conventional phototherapy versus micro-focused phototherapy**

Exposure to affected and unaffected skin areas	Treatment focused on skin lesions
Difficulty in treating certain skin areas (e.g. ear, nose) Slow delivery system, which needs longer treatment sessions	Possibility to treat difficult areas thanks to a manoeuvrable hand piece Quick delivery system. Treating only skin lesions, operators can also use higher doses of energy, achieving faster response on selected areas
Multiple and frequent visits to clinic Bulky machines	Shorten and less frequent visits Smaller device
Difficulty in treating claustrophobic patients and children, who may be afraid of the large device	Easy administration of the energy delivery and well tolerate - therapy

It consists of a short arc lamp generating a beam of visible, ultraviolet radiations, filtered to obtain only nb - UVB. BIOSKIN EVOLUTION® can provide a spectrum of intensity up to 400 mW/cm<sup>2</sup> and the peak of emission at 311 nm. The possibility to treat only vitiliginous patches, allows the operator to obtain lesional repigmentation, without an increase in the colour contrast between affected and not affected skin areas.

The therapeutic protocol (energy level, spot light, no. of the session, duration) is decided by the operator by patients' characteristics. The therapy is repeated once every three weeks, with the possibility to effect 2 sessions in the same day, for a total of 6 months.

Many data suggest how nb - UVB micro-focused phototherapy should be considered as first-choice therapy for localized vitiligo, where it may provide good clinical results in term of restoring pigmentation, patients' compliance, and safety [15][16].

## UVA - 1 therapy

Recently, light therapy lamps with halogen-metal band confined to the high irradiance UVA1 (340 - 400 nm) have experienced a growing interest and used in dermatology. The well-documented immunomodulating effects of UVA - 1, make this type of phototherapy useful for the treatment of several skin diseases, such as atopic dermatitis, psoriasis, vitiligo and other [17].

The therapeutic procedure schedules for vitiligo, usually, consists in 3 - 5 sessions per week, with a starting dose of 20 - 30 J/cm<sup>2</sup>, which is progressively increased in the following sessions to the full dose. The treatment is well tolerated. The most common side effects are tanning, erythema, pruritus and phototoxic reactions (eczema, urticaria). The long-term side effects are yet to be investigated [18].

## UVA - 1 target laser

Laser Alba 355® is an innovative, focused laser technology based on UVA - 1 spectrum with a wavelength of 355 nm (Table 4).

**Table 4: Clinical indication for Laser Alba 355®**

CLINICAL INDICATIONS
Atopic dermatitis
Dyshidrotic dermatitis
Psoriasis
Pityriasis rosea
Prurigo
Urticaria pigmentosa/Mastocytosis
Localized scleroderma (morphea)
Systemic lupus erythematosus
Lichen sclerosis
Mycosis fungoides and another T-cell lymphoma
Others: Vitiligo, Graft versus host disease, Granuloma annulare, Necrobiosis lipoidica, Cutaneous sarcoidosis, Follicular mucinosis, POEMS syndrome, Scleromyxedema, Hypereosinophilic syndrome, Pityriasis lichenoides

It consists of an active medium and a Neodymium - doped yttrium orthovanadate (Nd: YVO<sub>4</sub>) crystal that is "energetically pumped" by another laser with 808 nm wavelength. The light emitted by the Nd: YVO<sub>4</sub>, at a wavelength equal to 1064 nm, is impeded through an acoustic-optic crystal named Q - switch, producing a frequency of 20 - 50 kHz and transforming the laser light into an ultrashort pulsed light (25 nano sec). This pulse rate is higher than 40 kW, and it is sent to crystals to duplicate and triplicate the 1064 nm wavelength. Thus it produces a second (532 nm) and third (355 nm) harmonic wavelength delivery. The laser beam is then filtered by a harmonic separating mirror to select from this galvanometric head a 355 nm wavelength specific beam which is amplified and homogenate, before galvanometric head output, with a 2.5 mm spot and a pulse repeating potential up to 20.000 spots/second and designing variously shaped dimensional figures [19].

The use of Laser Alba 355® allows the treatment of selected affected skin areas so that the operator can use a more appropriate dose of energy, leading to shorter duration and less frequent treatment sessions. Time of emission and spot diameters are regulated by the operator, on the base of the clinical characteristic of individual patients. The treatment with Laser Alba 355® is well - tolerated. Acute side effects, such as erythema or pruritus, have rarely been described. Long-term side effects have yet to be determined.

## Immunomodulatory agent: Neovir®

Neovir® is an i.m. Immunomodulatory agent, composed of sodium oxo - dihydro - acridinyl - acetate (ODHAA).

Normally, it is used to normalise impaired

immune system functions under various conditions, such as viral infections, immunodeficiency, oncological diseases and multiple sclerosis. An experimental study evaluated the efficiency of acridone acetic acid, sodium salt, in stopping active nonsegmental vitiligo progression. Sixty patients with active non-segmental vitiligo have been treated with ten intramuscular injections, every 48 hours, of ODHAA. Vitiligo progression was assessed in 1, 3, 6 and 12 months after treatment. The results of the preliminary study were excellent: sodium oxodihydroacridinylacetate showed high efficiency in achieving long-term stabilisation of nonsegmental vitiligo [20].

## Melgain

In the last years, an Indian group of study developed a new topical drug (Melgain) for the treatment of vitiligo. It is a decapeptide derived from bFGF, which has to be applied topically once a day. Many data suggest how Melgain is effective in inducing repigmentation and particularly safe for treating children [21].

The combination of Melgain with target phototherapy has been demonstrated to be more effective.

## Antioxidants

It is now clear, how oxidative stress of both melanocytes and keratinocytes, is an important pathogenic mechanism at the base of vitiligo progression [22][23]. In particular, the impairment of keratinocytes removes the trophic support to melanocytes and induces their consequent death. Among the mechanisms that have been proposed in the prevention of keratinocyte cell stress, SIRT1 positive modulation has been recently suggested. On this observation, recently resveratrol and more innovative agents have been proposed and successfully tested in vitiligo patients, to protect them by the disease's progression.

## Low dose medicine (LDM)

Many studies underline how vitiligo is characterised by an unbalance of signalling molecules (e.g. growth factors, cytokines), that regulate the normal cross-talk between keratinocytes and

melanocytes. In details, vitiligo is characterised by a hyper production of Th1 and Th17-related cytokines, with an inflammatory action (e.g. TNF -  $\alpha$ , INF -  $\gamma$ , IL - 1, IL - 2, IL - 6, IL - 8, IL - 17). Recently, researchers and clinicians operating in the field of Low Dose Medicine (LDM) had investigated the possibility of treatment vitiligo with low dose cytokines, growth factors and neuropeptides. In details, it has been shown how the use of low oral dose anti-inflammatory cytokines (low dose Interleukin - 4 and Interleukin - 10; low dose anti-interleukin one antibody) and b - FGF, may be useful in restoring the altered keratinocytes-melanocytes cross-talk, leading to a skin repigmentation. The therapeutic protocol consists of the oral intake of 20 drops, twice a day, for 9 months of Low dose FGF, IL4, IL10 and IL1 [24][25].

Different observational studies demonstrated the efficacy and the safe profile of LDM in the treatment of vitiligo patients. The combination of the low dose cytokines with more conventional treatments (e.g. topical corticosteroids or micro-focused phototherapy) provide better results in term of repigmentation rate.

## Conclusion

Even if asymptomatic and not life threatening, vitiligo is a disease psychologically devastating that have to be treated. Today different types of therapies are available but none of them provide excellent results in term of repigmentation rate and safeness. For this reason, new studies and experiment have to be conducted.

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